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REMARKS

Claims 1-29 and 45-73 are pending in this application. Claims 1, 3, 8-9, 13-16, 19-20, 22-23, 26, 28, 45, 47,51-53, 57-60, 63-64, 66-67, 70 and 72 have been amended. Claims 2, 4-6, 46, and 48-50 have been canceled without prejudice or disclaimer. Support for these amendments can be found at least on pages 23-42. Applicant respectfully submits that no new matter has been added by way of these amendments.

Applicant submits herewith a Request for Continued Examination. An Information Disclosure Statement will be submitted shortly hereafter.

Claims 1, 13, 19, 45, 57, and 63 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to clearly set forth the metes and bounds of the patent protection desired. Applicant respectfully traverses the rejection and requests withdrawal of the same.

The Examiner alleges that "[e]xamples of how and when to prevent the risk of developing a menopause disorder are not set forth in the specification. . . . Examiner would favorably consider the term 'prophylaxis' over 'prevention.'"

Applicant has amended Claims 1 and 45 to recite, among other things, "A method for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder in a mammal in need thereof," as recommended by the Examiner. By amending these claims, Applicant does not acquiesce to the Examiner's argument but instead intends to expedite prosecution in this case.

Claims 13, 19, 57, and 63 have been amended to recite the particular material, "polyacrylic acid," for the trademark "CARBOPOL®," as recommended by the Examiner.

[redacted]

Applicant respectfully submits that the §112, second paragraph, rejections as being indefinite for failing to clearly set forth the metes and bounds of the patent protection has been overcome.

Claims 1-29 and 45-73 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention. Applicant respectfully traverses the rejection and requests withdrawal of the same.

The Examiner alleges that the expression "menopause disorders" in claims 1 and 45 renders the claims indefinite as to the disorders or conditions encompassed thereby.

Applicant explicitly defines the phrase "menopause disorder" in the application as filed on page 19, lines 26-34 and page 21, lines 7-29. Further, a person of ordinary skill in the art, at the time the present application was filed, would recognize other menopausal conditions that are encompassed by the expression "menopause disorders." (*See e.g.*, U.S. Patent No. 5,908,638). By utilizing the phrase "menopause disorders" in the claims, Applicant intends to cover those disorders and symptoms of a menopause disorder disclosed in the specification as well as other menopause disorders and symptoms that are generally know to a person of ordinary skill in the art.

In response to the Examiner's argument that the specification may not enable the treatment or prevention of specific cardiovascular disorders, Applicant respectfully submits that the specification provides for the treatment, prophylaxis or reduction of the risk of developing cardiovascular disorders, for example, by administering a "menopause disorder effective amount" of a sex hormone binding globulin synthesis inhibiting agent and a steroid.

Applicant respectfully submits that the §112, second paragraph, rejection as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention has been overcome.

Claims 1-29 and 45-73 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Rubin (US Patent 5,059,603), Ebert et al. (US Patent 5,152,997), and Place (US Patent 6,117,446) in view of Langtry et al. (Drugs 1999:57(6): 967-989), Remington's Pharmaceutical Sciences (1990, 18th ed., pages 1305 and 1314), Merck Index (11th ed., 1989, page 821, monograph 5103), Hofman et al. (US Patent 4,563,473), and Atkinson et al. (US Patent 4,442,094). Applicant respectfully traverses the rejection and requests withdrawal of the same.

As it now stands before the Patent Office, claim 1 recites, among other things, a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. Claims 2, 4- and 6 have been canceled without prejudice or disclaimer. Claims 3 and 7-29 depend directly or indirectly from independent Claim 1.

Claim 45 recites, among other things, a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering in a combination therapy methyltestosterone in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit, wherein the amount of the methyltestosterone and the steroid together make a menopause disorder effective amount. Claims 46 and 48-50 have been canceled without prejudice or disclaimer. Claims 47 and 51-73 depend directly or indirectly from independent Claim 45.

Rubin, Ebert et al, and Place in view of Langry et al., Remington's Pharmaceutical Sciences, Merck Index, Hofman et al., and Atkinson et al. do not teach or suggest the claimed invention. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. (MPEP 2143.01 citing In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)).

In the Background of the Invention, Rubin discloses that methyltestosterone has been administered subcutaneously or bucally in the past to treat impotence. Rubin then proceeds to teach away from using methyltestosterone as a sex hormone binding globulin synthesis inhibitor because it

> may cause severe toxic effects such as cholestatic jaundice[,] . . . additional pain, lack of complete absorption, and risk of deep and widespread infection. Additionally, long-term administration of [methyltestosterone] may inhibit endogenous testosterone formation and spermatogenesis by suppressing pituitary gonadotropin, resulting in glandular tissue atrophy because of disuse. Rubin, Col. 3, lines 1-11.

Rubin does not teach or suggest a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Ebert *et al.* teach a transdermal composition including testosterone and a permeation enhancer useful in treating male hypogonadism. However, Ebert *et al.* do not teach or a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit, and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Place recognizes that although androgens are mostly known for causing the masculinizing changes in males during puberty, low levels of androgens are also present in normal females. (See Place, Col.1, lines 17-21). Therefore, Place teaches the administration of an androgenic agent with a progestin and an estrogen in a buccal dosage unit to provide a complete hormone replacement therapy for women. Place does not teach or suggest a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit.

Applicant respectfully submits that none of the foregoing references teach or suggest, either alone or in combination, a method for the treatment, prophylaxis or reduction of the risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit as required in Claims 1 and 45.

The Examiner, then, cites the following references in arguing the obviousness of various claims that depend from Claim 1 or 45:

Langtry *et al.* teach that sildenafil is an oral therapy for erectile dysfunction.

Remington's Pharmaceutical Sciences teaches that ethanol may be used externally in astringents and anhidrotic lotions and as a solvent to cleanse the skin. Further, it teaches that carboxymethylcellulose sodium may be used in a tablet as a "pharmaceutic acid (suspending agent, tablet excipient or viscosity-increasing agent)."

The Merck Index teaches that isopropyl myristate may be used in topical medicinal preparations where good absorption through the skin is desired.

Hofman *et al.* teach sebum synthesis inhibiting compositions. The compositions may be in a gel form including an alcohol such as 2-propanol or ethanol, gel forming agents including but not limited to Carbopol, and penetration promoting agents including but not limited to isopropyl myristate.

Atkinson *et al.* teach that pharmaceutically acceptable carriers may include, among various other elements, lower alkanols, carboxymethylcellulose, isopropyl myristate, and carbopol.

Neither Langtry *et al.*, Remington's, Merck Index, Hofman *et al.*, nor Atkinson *et al.* teach or suggest, alone or in combination, a method for the treatment, prophylaxis or reduction of risk of developing a menopause disorder by administering a menopause disorder effective amount of methyltestosterone in an oral dosage unit and at least one pharmaceutically-acceptable steroid in a non-oral dosage unit. Neither do these references, either alone or in combination, teach the elements of Claims 1 or 45 that are missing from Rubin, Ebert et al., and Place.

Applicant respectfully submits that there is no motivation to combine the cited references to achieve the present invention. Virtually all inventions are combinations of old elements. In re Rouffet, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998). The Examiner has engaged in impermissible hindsight reconstruction by using the present application as a template for combining the cited references. Further, the Examiner has not identified any motivation to combine these references. To uphold a §103 rejection, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." Id.

Applicant maintains its arguments presented in the response to the Office Action dated February 8, 2002, that the Examiner does not cite any reference showing or suggesting the combination of these elements in the manner recited in Claims 1-29 and 45-73. Further, as disclosed on page 25, lines 15-28, a sex hormone binding globulin synthesis inhibitor, such as methyltestosterone, in combination with a percutaneously administered testosterone and/or estradiol produce a greater therapeutic effect than either alone and provide a means of increasing hormone concentrations in the bloodstream. Sex hormone binding globulin synthesis inhibitors, such as methyltestosterone, produce a decline in blood concentrations of sex hormone binding globulin. The decrease in sex hormone binding globulin subsequently causes an increase in free-hormone concentration for binding at the receptor. Transdermal application of an androgen, for example, testosterone, or an estrogen, for example, estradiol, bypasses first-pass metabolism and can provide a means of increasing hormone concentrations in the bloodstream. Thus, methyltestosterone and testosterone and/or estradiol produce a greater therapeutic effect than either entity alone because the decrease in hormone binding ability is coupled with an increased hormone bioavailability, producing higher free-hormone concentrations than would be produced by methyltestosterone alone, or testosterone alone, or estradiol alone.

need to show

The Examiner has not cited any pertinent references showing or suggesting to one of ordinary skill in the art the motivation to combine the elements as disclosed by the Applicant. The 35 U.S.C. § 103(a) rejection is therefore improper. Further, claims 3 and 7-29 depend on the patentability of claim 1 and claims 47 and 51-73 depend on the patentability of claim 45. If claims 1 and 45 are patentable, then so to are claims 3, 7-29, 47 and 51-73 regardless of whether other references teach their subject matter. Claims 2, 4-6, 46, and 48-50 have been canceled

without prejudice or disclaimer. Reconsideration and withdrawal of this 35 U.S.C. §103(a) rejection is requested.

CONCLUSION

With entry of the above Amendment and in view of the foregoing remarks, it is respectfully submitted that claims 1, 3, 7-29, 47 and 51-73 are in condition for allowance.

None of Applicant's amendments or cancellations are to be construed as dedicating any such subject matter to the public, and Applicant reserves all rights to pursue any such subject matter in this or a related patent application.

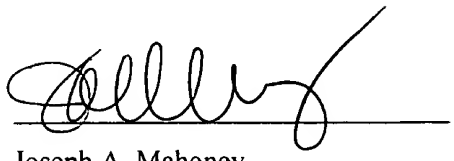
Submitted below is separate page titled "Version with Marking to Show Changes Made in the Claims," showing a marked-up copy of prior pending claims.

It is respectfully submitted in view of the foregoing Amendments and Remarks that all of the objections and rejections in the Office Action dated August 27, 2002 have been overcome and should be withdrawn. Applicant respectfully requests early and favorable notification to that effect.

If, in the opinion of the Examiner, a phone call may help to expedite prosecution of this application, the Examiner is invited to call Applicant's undersigned attorney at (312) 701-7174.

Respectfully submitted,

Dated: November 26, 2002

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE TO THE CLAIMS

1. (Twice Amended) A method [of treating, preventing or reducing] for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder in a mammal in need thereof, comprising administering to the mammal a menopause disorder effective amount of [a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent] methyltestosterone in an oral dosage unit, and at least one pharmaceutically-acceptable steroid selected from the group consisting of estradiol, testosterone, androstenedione, androstenediol, dehydroepiandrosterone, prenenolone, and dihydrotestosterone, and enantiomers, isomers, prodrugs or salts of the same in a non-oral dosage unit.

3. (Amended) The method of claim [2] 1, wherein the methyltestosterone is administered in the form of a tablet, capsule, cachet, lozenge, dispensable powder, granule, solution, suspension, emulsion or liquid.

8. (Amended) The method of claim 7, wherein the [androgen] testosterone is administered percutaneously.

9. (Amended) The method of claim 8, wherein the [androgen] testosterone is administered in the form of a hydroalcoholic gel.

13. (Amended) The method of claim 10, wherein the thickener is [CARBOPOL®] polyacrylic acid.

14. (Amended) The method of claim [4] 1, wherein the [estrogenic] steroid is estradiol.

15. (Amended) The method of claim 14, wherein the [estrogenic steroid] estradiol is administered percutaneously.

16. (Amended) The method of claim 15, wherein [the estrogenic steroid] estradiol is administered in the form of a hydroalcoholic gel.

19. (Amended) The method of claim 18, wherein the thickener is [CARBOPOL®] polyacrylic acid.

20. (Amended) The method of claim 1, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are each provided as a separate component of a kit.

22. (Amended) The method of claim 1, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are administered in a sequential manner.

23. (Amended) The method of claim 1, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are administered in a substantially simultaneous manner.

26. (Amended) The method of claim 1 [where the sex hormone binding globulin synthesis inhibiting agent comprises] , wherein the methyltestosterone is administered in an amount of about 0.2 mg to about 50.0 mg [methyltestosterone], and the steroid comprises testosterone administered in an amount of about 0.1 g to about 100.0 g [testosterone].

28. (Amended) The method of claim 1 [where the sex hormone binding globulin synthesis inhibiting agent comprises] , wherein the methyltestosterone is administered in an amount of about 0.2 mg to about 50.0 mg methyltestosterone, and the steroid comprises estradiol administered in an amount of about 0.1 g to about 100.0 g [estradiol].

45. (Twice Amended) A method [of treating, preventing or reducing] for the treatment, prophylaxis, or reduction of the risk of developing a menopause disorder in a mammal in need thereof, comprising administering to the mammal in a combination therapy [a pharmaceutically-acceptable sex hormone binding globulin synthesis inhibiting agent]

methyltestosterone in an oral dosage unit, and at least one pharmaceutically-acceptable [steroids] steroid selected from the group consisting of estradiol, testosterone, androstenedione, androstenediol, dehydroepiandrosterone, prenenolone, and dihydrotestosterone, and enantiomers, isomers, prodrugs or salts in a non-oral dosage unit, wherein the amount of the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid together make a menopause disorder effective amount.

47. (Amended) The method of claim [46] 45, wherein the methyltestosterone is administered in the form of a tablet, capsule, cachet, lozenge, dispensable powder, granule, solution, suspension, emulsion or liquid.

51. (Amended) The method of claim [50] 45, wherein the steroid is testosterone.

52. (Amended) The method of claim 51, wherein the [androgen] testosterone is administered percutaneously.

53. (Amended) The method of claim 52, wherein the [androgen] testosterone is administered in the form of a hydroalcoholic gel.

57. (Amended) The method of claim 54, wherein the thickener is [CARBOPOL®] polyacrylic acid.

58. (Amended) The method of claim [48] 45, wherein the [estrogenic] steroid is estradiol.

59. (Amended) The method of claim 58, wherein the [estrogenic steroid] estradiol is administered percutaneously.

60. (Amended) The method of claim 59, wherein the [estrogenic steroid] estradiol is administered in the form of a hydroalcoholic gel.

63. (Amended) The method of claim 62, wherein the thickener is [CARBOPOL®] polyacrylic acid.

64. (Amended) The method of claim 45, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are each provided as a separate component of a kit.

66. (Amended) The method of claim 45, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are administered in a sequential manner.

67. (Amended) The method of claim 45, wherein the [sex hormone binding globulin synthesis inhibiting agent] methyltestosterone and the steroid are administered in a substantially simultaneous manner.

70. (Amended) The method of claim 45 [where the sex hormone binding globulin synthesis inhibiting agent comprises] , wherein the methyltestosterone is administered in an amount of about 0.2 mg to about 50.0 mg [methyltestosterone], and the steroid comprises testosterone administered in an amount of about 0.1 g to about 100.0 g [testosterone].

72. (Amended) The method of claim 45 [where the sex hormone binding globulin synthesis inhibiting agent comprises] , wherein the methyltestosterone is administered in an amount of about 0.2 mg to about 50.0 mg methyltestosterone, and the steroid comprises estradiol administered in an amount of about 0.1 g to about 100.0 g [estradiol].